Summary Review for Regulatory Action

Date	November 30, 2011
From	Andrea Leonard-Segal, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # Supplement #	21-998/S002
Applicant Name	Teva Women's Health, Inc.
Date of Submission	February 7, 2011
PDUFA Goal Date	December 7, 2011
Proprietary Name / Established (USAN) Name	Plan B® One-Step / levonorgestrel
Dosage Forms / Strength	Tablet / 1.5 mg
Proposed Indication(s)	Reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Christina Chang, M.D., 10/5/2011
Statistical Review	Rima Izem, Ph.D., 10/12/2011
Social Scientist Review Plan B® One-Step	Oluwamurewa, Oguntimein, M.S., 07/25/2011
Social Scientist Review Plan B®	Karen Lechter, J.D., Ph.D. 11/05/03
OSI Review	Sharon K. Gershon, Pharm.D., 09/23/2011
Labeling Reviews	Maria Ysern, M.Sc., Colleen Rodgers, Ph.D., 09/29/11, 10/27/11 and 11/16/11
CDTL Review for NDA 21-998/S002	Lesley-Anne Furlong, M.D., 10/25/2011
CDTL Review for NDA 21-998	Lisa M. Soule, M.D. 07/09/2009
OSE Reviews	1. Mark Miller, Pharm D., Adrienne Rothstein, Pharm D., Linda Scarazzini, M.D., 11/10/11 2. Teresa Rubio, Daniel Davis, M.D., Audrey Gassman, Robert Boucher, M.D. 915 review 06/13/2011 3. Mark Miller, Pharm.D., Melissa Truffa R. Ph., Robert Boucher,M.D. , Gerald Dal Pan, M.D., 06/19/09 Plan B® (levonorgestrel), NDA 21-045. 4. Adrienne Rothstein, Pharm D. and Melissa Truffa R.Ph., 04/07/08 NDA 21-045.
Pediatric and Maternal Health Staff Consult	Lisa Mathis, M.D., 10/11/2011

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

On February 7, 2011, Teva Women's Health, Inc. (Teva) submitted an efficacy supplement to NDA 21-998 that provides data intended to support the marketing of Plan B® One-Step (levonorgestrel 1.5 mg) as a nonprescription product to all women of reproductive potential without an age restriction. Plan B® One-Step has been found to be a safe and effective emergency contraceptive (EC) for all women of reproductive age. Currently, Plan B® One-Step is available as a nonprescription product for women ages 17 years and older. The younger population in need of ECs must obtain a prescription before they can purchase the medication. The different marketing status for these different age groups reflects the complicated regulatory history of levonorgestrel as an emergency contraceptive.

To support this efficacy supplement Teva has submitted the following information:

- Label Comprehension Study (Study DR-LEV-301)
- Actual Use Study (Study DR-LEV-301)
- Literature Review
- Analysis of Postmarketing Safety Data
    - Teva's postmarketing database
    - FDA's Adverse Event Reporting System (AERS)
    - World Health Organization's International Drug Monitoring Program (WHO)
    - Drug Abuse Warning Network (DAWN)
    - American Association of Poison Control Centers data (AAPCC)
    - 120-Day Safety Update
- Proposed Labeling

This review will address the new efficacy supplement in the context of the regulatory history of Plan B® and Plan B® One-Step.

2. Background

Levonorgestrel is a second generation progestin derived from norgestrel. It has been available in hormonal contraceptive products for decades. Among the approved levonorgestrel-containing products are Plan B®, levonorgestrel 0.75 mg, and Plan B® One-Step, levonorgestrel 1.5 mg. Both of these are orally administered ECs and tens of millions of the products have been sold in the United States since they were approved. Data from Teva indicates that from July 2009 (when Plan B® One-Step was approved) though January 2011 a total of [redacted] units of Plan B® were distributed and, excluding non-profit clinics, [redacted] units were distributed commercially. Of these, [redacted]% of prescriptions were for patients 16 years of age and younger. (These data do not account for generic sales of levonorgestrel EC.) For Plan B® One-Step, [redacted] units were distributed by Teva of which [redacted] were

commercially distributed units ([redacted]%). Prescriptions for patients 16 years of age and younger accounted for [redacted]% of the commercially distributed units.

The exact mechanism of action for levonorgestrel as an emergency contraceptive is not known. Levonorgestrel is thought to act by delaying ovulation post-coitally by impairing follicular maturation and disrupting mechanisms involved in the luteinizing hormone surge. Postovulatory mechanisms of action may include such things as interference with fertilization resulting from changes in cervical mucus and uterine fluid that impede sperm penetration and migration. The effect of Plan B One-Step, if any, on implantation of a fertilized egg is unknown. There is no medical evidence that levonorgestrel can impact the course of a pregnancy once implantation has occurred; there is no medical evidence that Plan B® One-Step or Plan B® would harm a developing baby.

Plan B® was initially approved in the United States as a prescription-only EC on July 28, 1999. The treatment regimen for Plan B® consists of two doses; the first 0.75 mg tablet is to be taken as soon as possible within 72 hours of having unprotected sexual intercourse or a known or suspected contraceptive failure and the second tablet is to be taken 12 hours later. This product was approved for over-the-counter (OTC) marketing for women ages 18 and older on August 24, 2006 via NDA 21-045/S-011. It remained a prescription (Rx) product for females 17 years of age and younger. At the time of the partial OTC switch, Plan B® was approved as a single package configuration for dual prescription and nonprescription (OTC) marketing. Since the carton bore the statement "Rx only for age 17 and younger," the product was required to be kept behind the pharmacy counter and/or distributed by licensed practitioners. The Plan B® OTC population was expanded to include 17-year-old women in 2009 under an efficacy supplement. This occurred on the same day that NDA 21-998 for Plan B® One-Step (a single levonorgestrel 1.5 mg tablet dosing regimen) was approved OTC for women ages 17 and older and by prescription for those less than 17 years of age. A single package configuration for dual prescription and OTC marketing was then the situation for both Plan B® and for Plan B® One-Step.

The regulatory histories of the OTC approvals for Plan B® (NDA 21-045) and Plan B® One-Step (NDA 21-998) have been interwoven and complex. Several sponsors/applicants have been involved along the way as ownership of the products has changed hands (Women's Capital Corporation, Barr Research, Inc, Duramed Pharmaceuticals, Inc., Teva Women's Health, Inc.). In her review, Dr. Christina Chang has nicely distilled the regulatory history as it applies to this Plan B® One-Step efficacy supplement. I will highlight certain parts of the regulatory history here.

In April 2003 Barr Research, Inc. (Barr) submitted a supplement to NDA 21-045 to switch Plan B® (levonorgestrel 0.75 mg) OTC for all women of reproductive age. In 2004, this application was presented at a joint meeting of the Nonprescription Drug Advisory Committee and the Advisory Committee for Reproductive Health Drugs. The committee recommended that the NDA supplement should be approved OTC for all ages (by a vote of 23 to 4). So did all of the FDA primary and secondary review staff (with the exception of one medical officer in the Division of Over-the-Counter Drug Products), the Deputy Directors of the involved FDA divisions, Drs. Rosebraugh and Griebel (who had been delegated responsibility for the

application) and the directors of the Offices involved in the application (Drs. Jonca Bull, Florence Houn, and John Jenkins). Dr. Stephen Galson, then the acting director of the Center for Drug Evaluation Research (CDER), disagreed with the recommendations for approval and in May, 2004 issued a Not Approvable letter because of the "lack of available data relevant to OTC use of the product by adolescents younger than 14 and very limited data in the 14 – 16 age group."

Two months later, the applicant submitted a Complete Response to the Not Approvable letter in which they proposed to switch Plan B® to OTC status for women 16 years of age and older. In an August 26, 2005 memorandum, Dr. Steven Galson, Director, CDER, concluded that the label comprehension and actual use data submitted with the application supported OTC use of Plan B® by women aged 17 years and older, but not by females ages 16 years and younger. Additional data would be needed in the younger population. On the same date, Commissioner Crawford signed a letter telling the applicant (at this point, Duramed Pharmaceuticals, Inc. (Duramed)) that their product could not be legally marketed OTC in the United States and that FDA had decided to publish an advance notice of proposed rulemaking asking for public comments on when an active ingredient can be simultaneously marketed in both a prescription and an OTC drug product and also on questions related to the marketing of Rx and OTC versions of the same active ingredient in a single package.

In a letter dated July 31, 2006, Dr. Andrew von Eschenbach, then Acting Commissioner of FDA, informed the sponsor that the Agency had determined that "it is not necessary to engage in rulemaking to resolve the novel regulatory issues raised by your application." Dr. von Eschenbach further indicated that the Agency would like to meet with Duramed to discuss resumption of review of their sNDA for the Rx to OTC switch of Plan B® for emergency contraception in women 18 years of age an older.

Duramed subsequently met with the Agency on August 8, 2006. During that meeting issues related to the age cutoff for OTC marketing and the sponsor's proposed Convenient Access, Responsible Education Program (CARE$_{SM}$) were discussed. The CARE$_{SM}$ Program was constructed to help ensure that when Plan B® was OTC for one age group and prescription for another that it would be provided responsibly and appropriately. Duramed resubmitted their application on August 17, 2006 and included revised prescription and OTC labeling for Plan B® along with a revised CARE$_{SM}$ Program. Dr. Andrew von Eschenbach wrote, in a memorandum dated August 23, 2006, that the scientific data supported an OTC indication for women aged 17 years and older. However, he stated:

"In considering the difficulty of enforcing an age-based restriction on the availability of this oral hormonal contraceptive, I have concluded that 18 (rather than 17) is the more appropriate cutoff point to best promote and protect the public health. The state-regulated pharmacies that will be dispensing Plan B® under Barr's voluntary CARE$_{SM}$ program (as well as society as a whole) are more familiar with 18 as a cutoff age. I understand that in all 50 states, 18 is the age of majority (i.e., the legal delineation between minor and adult), and retail outlets, including pharmacies, are familiar with using 18 as the age restriction for the sale of certain products……This approach builds on well-established state and private-sector infrastructures to restrict certain products to consumers 18 and older……Here, Barr's

CARE℠ program specifically utilizes state-licensed pharmacies to implement its restricted distribution plan. Given this fact, and the existing experience pharmacies have enforcing the age-based restriction of 18, I have determined that to best protect and promote the public health nonprescription Plan B® should be available for ages 18 and above."

Plan B® was approved OTC for women ages 18 years and older on August 24, 2006. It remained available by prescription for those less than 18 years of age. As Dr. Furlong points out in her review, Plan B® thus became the only FDA-approved contraceptive product with OTC labeling for a subset of women for reproductive age. In contrast, condoms and spermicides have a long history of OTC availability without regard to age.

Between 2007 and 2010, FDA had a variety of meetings (internal and with the sponsor) and other communications with Duramed regarding the data needed to support the unrestricted OTC availability of Plan B® and Plan B® One-Step. Dr. Galson, Dr. Jenkins, others from management and representatives from the Pediatric and Maternal Health Staff participated in some of those discussions and provided input into to the trial design requirements for label comprehension and actual use studies to be conducted in adolescents. Thus, when I signed letters advising the sponsor as to study parameters such as how many young people of each age to enroll in the trials, much of this advice had been vetted by others higher in the Agency than I and by our pediatric consultants so we were sure the advice addressed Dr. Galson's concerns.

On January 12, 2009, Duramed submitted NDA 21-998 to support the nonprescription approval of Plan B® One-Step for women at least 18 years of age and the prescription approval for women less than 18 years old. (This was the second round of FDA review for this application.) During the course of the review, on March 23, 2009, the U.S. Federal District Court Judge Edward Korman (in the case of *Tummino v. von Eschenbach et al*) issued an order directing the FDA to permit Duramed to make Plan B® available to women ages 17 years and older without a prescription within 30 days. In addition, he ordered FDA to reconsider its decisions regarding the Plan B switch to OTC use.

On April 21, 2009, I signed a letter to Duramed on behalf of FDA and in alignment with the court order which said,

"As you were advised in a letter dated August 26, 2005, the Center for Drug Evaluation and Research concluded that the available scientific data were sufficient to support the safe use of Plan B® as a nonprescription product for women who are 17 years or older. When FDA made the determination in 2006 to approve nonprescription availability for women 18 years or older, the reason provided for not approving nonprescription access for 17-year-old women was a concern expressed by the Commissioner about the ability of pharmacies (and thus their professional staffs) to enforce the age restriction with respect to purchases by women under age 17 without a prescription.

The Center has been authorized to handle this application using the same procedures as for other drugs, as described in the current delegation procedures. Therefore, as the Division Director, I have now considered whether the enforceability concerns expressed by the

Commissioner necessitate an age restriction to women 18 years of age and older for nonprescription use as opposed to a restriction to women 17 years of age and older. I am unaware of data that support a distinction between ages 17 and 18 in terms of enforceability of an age restriction. Data recently submitted by you regarding your Convenient Access, Responsible Education (CARE) program, under which you have monitored compliance with the current prescription age requirement, support the fact that pharmacists do check identification for the age restriction as it exists today. I have no reason to doubt that pharmacists are capable of accurately determining the age of women seeking to purchase Plan B® without a prescription by reviewing identification and providing Plan B® according to the conditions of approval as related to age. I therefore conclude that Plan B® may be made available to women 17 years and older without a prescription."

The letter also said that if Duramed wanted to pursue marketing of Plan B® for women 17 years of age and older without a prescription but prescription only for women 16 years and younger, they would need to submit revised draft labeling as a prior approval efficacy supplement to NDA 21-045 that would allow for this change in population. Additionally, in the letter, FDA told Duramed that if they wanted to pursue the marketing of Plan B® for women 17 years of age and older without a prescription, or other options for marketing Plan B®, that FDA encouraged a meeting to discuss necessary labeling revisions and the content of any submission(s).

On June 1, 2009, Duramed met with FDA to discuss the pathway to a full OTC switch for both the Plan B® and Plan B® One-Step products. At that meeting, Duramed explained that any future drug development plans would be dependent upon the decisions of Teva management. Duramed stated that any decision regarding changes to the labeled population, beyond an OTC switch for women 17 years of age, would occur after the July 12, 2009 PDUFA goal date for NDA 21-998. FDA and Duramed agreed that, for NDA 21-045, the sponsor would provide an efficacy supplement with revised labeling and a safety update to support OTC access down to 17 years of age. Similarly, the sponsor would amend NDA 21-998 for Plan B® One-Step by providing revised labeling for OTC access to 17 years of age and also the requisite safety update. Within two weeks, Duramed submitted all of this material and on July 10, 2009 both products were approved OTC for women down to age 17.

Now, with this new efficacy supplement, Teva seeks OTC availability of Plan B® One-Step for all women of reproductive age. Teva is not currently marketing Plan B® in the United States, so the company is not seeking the same marketing status for that product. There are two companies (Watson and Perrigo) that currently market generic versions of Plan B® in the U.S.

3. CMC/Device

There were no new chemistry data required for this efficacy supplement. The drug product and the packaging are identical to the approved product.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology issues were raised in this efficacy supplement [redacted]

5. Clinical Pharmacology/Biopharmaceutics

There are no new clinical pharmacology/biopharmaceutics issues raised by this efficacy supplement [redacted]

6. Clinical Microbiology

There were no clinical microbiology data required [redacted] for this efficacy supplement.

7. Clinical/Statistical-Efficacy

The efficacy of Plan B® One-Step was established for all females of reproductive age for the original NDA approval. The product is approved both as an OTC and as a prescription drug based upon these efficacy data that demonstrated the prevention of an acceptable fraction of pregnancies (83.95%) when the product is used within 72 hours of unprotected coitus. Therefore, no new clinical efficacy data were needed to support the approval of this efficacy supplement to switch the product from prescription to OTC for young women < 17 years of age.

8. Safety

Study DR-LEV-301: Label Comprehension Study (LCS)
For the detailed analysis of the Label Comprehension Study the reader is referred to the Social Scientist review by Oluwamurewa Oguntimein and the statistical review by Dr. Rima Izem. [redacted]

This was an open-label, non-comparative multi-center study designed to estimate the proportion of young women aged 12-17 years who understood each of the following key elements of the Plan B® One-Step labeling:

1. Plan B® One-Step is indicated for prevention of pregnancy after unprotected sex
2. Plan B® One-Step should be taken as soon as possible after sex
3. Plan B® One-Step does not prevent sexually transmitted diseases or HIV/AIDS
4. Plan B® One-Step should not be used in place of regular contraception

5. Plan B® One-Step should be taken within 72 hours after sex
6. Plan B® One-Step should not be used by women who are already pregnant

Two to four questions were posed to test each element. Three hundred seventy-seven subjects were recruited of whom 335 met all inclusion criteria and comprised the primary analysis population. They were recruited at eight shopping malls (n = 290) and family planning clinics sites (n = 45) spread across the United States. Minimum quotas were pre-specified to ensure diversity by age, race, literacy, and prior EC use. The quotas for race and ethnicity were based on U. S. census data from the year 2000; the quota for literacy was based on the 2002 National Assessment of Adult Literacy.

The planned analysis was the proportion of subjects who understood each key concept for the overall population and for a variety of predefined subgroups. The sample size for each age range, other subgroup quotas, and the elements of labeling to test were negotiated with the FDA before the study started.

The pre-specified demographic quotas were met and exceeded. The eligible population included between 54 and 59 subjects of each age between 12 and 17 years of age (see Table 1). The FDA had requested that the sponsor enroll at least 50 of each age. Among the eligible population, 21% were Hispanic, 26% were African Americans, and 42% were low literate defined as reading at a 7th grade level or less (as assessed with a score of 58 or below on the Rapid Estimate of Adult Literacy in Medicine – Teen instrument). Seven percent reported previous use of emergency contraceptive pills, although the protocol allowed for up to 25%.

Table 1. Eligible Population by Age Group

Age	N
12	54
13	56
14	54
15	59
16	57
17	55
Total	335

Source: Dr. Furlong's review

Table 2 demonstrates that the least well understood concept was that Plan B® One-Step should be taken as soon as possible after sex (82.7%). (While recognizing differences in methodology and the hazards of cross-study comparisons, in the label comprehension study for Plan B® which supported the OTC switch for women at least 18 years of age, the comprehension rate for this communication objective was also 82%.) The other concepts were understood by ≥ 89.6%. [redacted]

Table 2. Study Subjects Understanding of Key Concepts

Key Concepts	Subjects who understand n (%) N=335	95% CI
1. 1. Plan B® One-Step is indicated for prevention of pregnancy after unprotected sex	300 (89.6%)	(86%, 93%)
2. Plan B® One-Step should be taken as soon as possible after sex	277 (82.7%)	(78%, 87%)
3. Plan B® One-Step does not prevent sexually transmitted diseases or HIV/AIDS	310 (92.5%)	(89%, 95%)
4. Plan B® One-Step should not be used in place of regular contraception	309 (92.2%)	(89%, 95%)
5. Plan B® One-Step should be taken within 72 hours after sex	319 (95.2%)	(92%, 97%)
6. Plan B® One-Step should not be used by women who are already pregnant	320 (95.5%)	(93%, 97%)

Source: Adapted from Dr. Izem's review

Table 3 shows that the understanding of key concepts was similar regardless of the age of the adolescent. Key concept #2, related to timing of pill ingestion, trends to being less well understood by 12- and 13-year-olds. [redacted] The scenario-based question was, "Ellie had unprotected sex on Thursday afternoon. That night, she thought about taking Plan B 1.5. She could have gotten it right then, but she decided to wait until Saturday to buy it. According to the box, when was the best time to take it: (1) Thursday night (b) Saturday, or (c) it doesn't matter." The social scientist review provides the following analysis of this question and the responses to it.

[redacted]

[redacted]

[redacted] In response to the LCS results, with this efficacy supplement the sponsor has added prominent text to the proposed label to emphasize the importance of taking Plan B® One-Step as soon as possible.

Table 3. Understanding of Key Concepts by Age

	Age					
	12 N= 54 %	13 N= 56 %	14 N= 54 %	15 N= 59 %	16 N=57 %	17 N=55 %
1. Plan B® One-Step is indicated for prevention of pregnancy after unprotected sex	87	82	85	95	91	96
2. Plan B® One-Step should be taken as soon as possible after sex.	78	77	83	88	83	87
3. Plan B® One-Step does not prevent STDs or HIV/AIDS	91	88	87	98	95	96
4. Plan B® One-Step should not be used in place of regular contraception	93	88	91	93	93	96
5. Plan B® One-Step should be taken within 72 hours after sex.	98	89	89	98	98	98
6. Plan B® One-Step should not be used by women who are already pregnant	94	95	91	98	97	98

Source: Dr. Furlong's review

White participants trended toward understanding the key concepts somewhat better than African Americans and others but the success rates across all groups were quite good. (See Table 4.) Hispanic ethnicity did not seem to impact label comprehension, except possibly for a trend toward greater understanding of key concept #2 among Hispanics. (See Table 5.) Lower literate subjects trended toward less understanding of all six key concepts (See Table 6.) Subjects who had prior experience with emergency contraceptives tended to have somewhat better comprehension of key concepts than subjects who had never used ECs. Table 7.)

Table 4. Understanding of Key Concepts by Race

	Race		
	White only	African American	Other
	N= 163 %	N= 88 %	N=74 %
1. Plan B® One-Step is indicated for prevention of pregnancy after unprotected sex	95	88	89
2. Plan B® One-Step should be taken as soon as possible after sex.	90	73	87
3. Plan B® One-Step does not prevent sexually transmitted diseases or HIV/AIDS.	97	91	92
4. Plan B® One-Step should not be used in place of regular contraception	97	90	92
5. Plan B® One-Step should be taken within 72 hours after sex.	98	94	100
6. Plan B® One-Step should not be used by women who are already pregnant	98	98	96

Source: Dr. Furlong's review

Table 5. Understanding of Key Concepts by Ethnicity

	Hispanic N= 70 %	Non-Hispanic N= 254 %
1. Plan B® One-Step is indicated for prevention of pregnancy after unprotected sex	93	92
2. Plan B® One-Step should be taken as soon as possible after sex.	93	83
3. Plan B® One-Step does not prevent STDs or HIV/AIDS	94	95
4. Plan B® One-Step should not be used in place of regular contraception	93	94
5. Plan B® One-Step should be taken within 72 hours after sex.	100	97
6. Plan B® One-Step should not be used by women who are already pregnant	97	98

Source: Dr. Furlong's review

Table 6. Understanding of Key Concepts by Literacy Level

	Literacy Level	
	7th grade or lower N= 140 %	8th grade or higher N= 195 %
1. Plan B® One-Step is indicated for prevention of pregnancy after unprotected sex	82	95
2. Plan B® One-Step should be taken as soon as possible after sex.	74	89
3. Plan B® One-Step does not prevent STDs or HIV/AIDS	84	99
4. Plan B® One-Step should not be used in place of regular contraception	87	96
5. Plan B® One-Step should be taken within 72 hours after sex.	92	97
6. Plan B® One-Step should not be used by women who are already pregnant	92	98

Source: Dr. Furlong's review

Table 7. Understanding of Key Concepts by Ever Use of Emergency Contraceptive Pills,

	Prior use N= 24 %	Never used N= 311 %
1. Plan B® One-Step is indicated for prevention of pregnancy after unprotected sex	100	89
2. Plan B® One-Step should be taken as soon as possible after sex.	83	83
3. Plan B® One-Step does not prevent sexually transmitted diseases or HIV/AIDS	100	92
4. Plan B® One-Step should not be used in place of regular contraception	96	92
5. Plan B® One-Step should be taken within 72 hours after sex.	100	95
6. Plan B® One-Step should not be used by women who are already pregnant	100	95

Source: Dr. Furlong's review

Teva also provided a comparison between Study DR-LEV-301 and the LCS done in 2001 for the Plan B® application. The 2001 study included 656 subjects from 12 to 50 years old, of whom 580 were 17 years and older. The 2001 study was of similar design and 13 questions in both studies overlapped. The proportions of subjects who answered correctly were similar for 11 of 13 questions. In the two questions with the greatest difference between groups, the older subjects had a greater percentage of incorrect responses. Both of these questions were related to the instruction to take the tablets as soon as possible after sex.

[redacted]

[redacted] Dr. Lisa Mathis, Associate Director of the Pediatric and Maternal Health Staff in the Office of New Drugs, did not express concerns with the study or the results.

[redacted]

The actual use study is reviewed in detail in Dr. Chang's primary clinical review and was also assessed by Drs. Furlong and Mathis. [redacted]

The AUS was an open-label, single-arm, naturalistic study to determine the percentage of subjects who correctly self-select and use Plan B® One-Step under simulated OTC conditions. The two primary objectives of the study were:

- to determine the percentage of subjects who appropriately self-selected
- to determine the proportion of subjects who correctly used Plan B® One-Step under simulated OTC conditions

Correct self-selection was defined as wanting to use the product for its indication AND not having an allergy to levonorgestrel, a positive pregnancy test, or a known pregnancy. Correct use was defined as taking Plan B® One-Step within 72 hours following unprotected sex. The secondary objectives were to estimate the incidence of adverse events and repeat use of emergency contraception during the 8-week follow-up period.

The study sought to enroll subjects 11 to 17 years old who were seeking emergency contraception (EC). The setting mimicked the OTC environment in that subjects who had self-diagnosed the need for EC presented to the clinic study sites spontaneously requesting EC and obtained Plan B® One-Step without the intervention of a healthcare provider. Each subject who met the inclusion criteria (age, need of EC for herself, ability to read English, and willingness to participate in the study) read the product label without assistance. A pre-approved script controlled the information that study staff could provide. Only those subjects who appropriately self-selected (as assessed via a self-administered Participation Questionnaire following the self-selection decision) received study medication. Subjects who inappropriately self-selected were referred to clinic staff for further assessment and treatment.

Follow-up occurred at one, four, and eight weeks, and weekly thereafter if needed for adverse events or pregnancies. Subjects were asked about product use, health problems since last contact, and pregnancy status. Subjects were also asked about repeated use of EC since enrollment, and charts were evaluated for repeat use as well.

The sample size (which had been negotiated with FDA) was to include a minimum of 25 females of each age, 14 through 17 years, and any subjects from 11 to 13 years who were eligible to participate. The originally agreed-upon number of subjects in the 11- to 13-year age range was 25, but, after two years of study experience, enrollment in that age range was minimal (only three subjects aged 13 and none younger than 13). FDA agreed to a protocol amendment to continue to enroll 11- to 13-year olds without a minimum number of enrollees [redacted] Refer pages 49-50 of Dr. Chang's review for the details. When Plan B® One-Step was approved in July 2009 as an OTC product for women 17 years of age and older, the AUS protocol was amended to no longer recruit 17-year-olds.

Results:

Enrollment was slow because the Actual Use Study was initiated prior to the approval of Plan B® One-Step, while the drug was still an investigational product. However, the University of California, San Francisco site was able to enroll study participants during that period. After the drug was approved, Teva increased the number of participating sites and ultimately, there were five geographically dispersed clinical investigation sites; however, the one at the University of California still enrolled the vast majority of the study participants (316 of 343 total subjects). The fact that the University of California site enrolled a diverse, representative population

makes the study population enrolled in this trial acceptable [redacted]

Table 8 depicts the age range of enrolled subjects. It is important to point out that clinics were unable to enroll any subjects younger than 13 years of age because none presented for emergency contraception. As Dr. Mathis comments in her review, the low number of adolescents from ages 11 – 13 years old is consistent with the known use of these products in this age group. She states, "The condition and the response to therapy in patients in this age group is expected to be sufficiently similar to patients in the 14-year-old age group and thus data from that age group can be used to support the ability of younger patients to use the medication appropriately." While there were few enrollees less than 14 years old, the LCS enrolled 50 subjects aged 12 and 50 aged 13 and their comprehension of the label was good. (Refer back to Table 3.) The race distribution was 42.9% Latina, 19.8% Asian/Pacific Islanders, 14.0% African-American, and 11.4% White.

Approximately 40% of subjects had used EC previously, with the percentage increasing with age (ranging from 0% of 13-year-olds, to 66.2% of 17-year-olds). As shown in Table 8, approximately 29.4% of subjects reported no previous use of contraception with the percentage decreasing with increasing age (66.7% of 13-year-olds to 15.4% of 17-year-olds). Approximately 88.3% had never been pregnant, with the percentage decreasing with increasing age (100% of 13-year-olds to 81.5% of 17-year-olds).

Table 8. Number of Subjects and Prior Use of Contraception by Age in AUS

Age of Subjects	13 years old	14 years old	15 years old	16 years old	17 years old
N	3	35	100	140	65
No previous use of contraception	66.7%	51.4%	31%	28.6%	15.4%

Source: Applicant's Submission, Clinical Study Report, Table 8

By the applicant's analysis, results of the primary objectives for the enrolled population were:

- 90.1% appropriately self-selected
- 88.6% of those who appropriately self-selected correctly used the product within 72 hours of intercourse

[redacted]

[redacted]

In Dr. Chang's review, she considered only two subjects of the 343 to be inappropriate self-selectors because they had positive pregnancy tests at the time of self-selection. This means that there was a > 99% correct self-selection rate. [redacted]

[redacted] Dr. Chang points out that, concerns regarding cross-study comparisons notwithstanding, adult and adolescent subjects appear to have used EC comparably well in these two studies [redacted].

Table 9 and Table 10 show exploratory analyses of the primary endpoint by age. [redacted]

Table 9. Proportion of Enrolled Population that Appropriately Self-Selected by Age (Years)

	13	14	15	16	17
Number of Subjects	3	35	100	140	65
Appropriate Self-Selection	2 (66.7%)	30 (85.7%)	91 (91.0%)	128 (91.4%)	58 (89.2%)

Source: Applicant's Submission, Clinical Study Report, Table 18

Table 10. Proportion of Treated Population Demonstrating Correct Product Use Within 72 Hours after Intercourse by Age (Years)

	13	14	15	16	17
Number of Subjects	1	30	87	123	56
Product Use within 72 Hours	1(100%)	24 (80.0%)	78 (89.7%)	107 (87.0%)	53 (94.6%)

Source: Applicant's Submission, Clinical Study Report, Table 19

[redacted]

[redacted]

A secondary objective was measuring the repeat use of emergency contraception during the 8-week follow-up period. Most subjects reported a single use of Plan B® One-Step during the study. Table 11 summarizes a subgroup analysis by age. [redacted] Repeat use included one additional time (13.7%), two additional times (5.7%), or three additional times (0.7%).

Table 11. Repeat Product Use in the Completed Follow-Up Population (N=277) by Age (Years) at Screening

Number of repeat uses	13	14	15	16	17
None	1 (100%)	22 (84.6%)	64 (78.1%)	92 (81.4%)	45 (81.8%)
1	0	1	12	19	6
2	0	3	6	3	4
3	0	0	1	1	0

Source: Applicant's Submission, Clinical Study Report, Table 28

[redacted]

Adverse Events (AEs): Of the 297 subjects who took study drug, 43 reported a total of 70 AEs. There were no deaths and one serious adverse event was reported (a miscarriage). [redacted] The most frequently reported adverse events were nausea, headache, and menstrual irregularity. (Refer to Table 12.)

Table 12. Frequency of Reported Adverse Events in ≥ 1% of the Safety Population: Subjects Who Reported Any Use of Plan B® One-Step

Adverse Event (MedDRA Preferred Term)	Total Number of Subjects = 299 N (%)
Nausea	8 (2.7%)
Headache	8 (2.7%)
Menstruation Irregular	6 (2.0%)
Vaginal Bleeding*	4 (1.3%)
Pelvic Pain	4 (1.3%)
Influenza	3 (1.0%)
Vulvovaginal Mycotic Infection	3 (1.0%)
Vaginal Spotting*	3 (1.0%)
Dizziness	3 (1.0%)
Abdominal Pain Upper	3 (1.0%)
Fatigue	3 (1.0%)
Vomiting	3 (1.0%)

*Vaginal Bleeding, regardless of severity, codes in MedDRA to a Preferred Term of "Vaginal Haemorrhage." Therefore, for clarity, the applicant used the MedDRA Lower Level Term rather than the Preferred Term
Source: Applicant's Submission, Clinical Study Report, Table 29

Subjects reported seven pregnancies, one of which was reported by investigators as a serious adverse event (the miscarriage). The pregnancy data are summarized in Table 13.

Table 13. Summary of Pregnancies Among the 297 Subjects Who Took Plan B® One-Step

Site/Subject	Age (Years)	Used Plan B® within 72 hours of unprotected intercourse	Comments	Outcome
1/0107	16	Yes (one day after unprotected sex)	By 8-week ultrasound, conceived on or shortly after the index episode of unprotected sex	Surgical termination
1/0131	14	Yes (one day after episode of unprotected sex for which she presented to the clinic)	By 13-week ultrasound, was about 1 week pregnant when she took Plan B® One-Step (too early for self-diagnosis or positive pregnancy test). Information was not provided to clarify if she had another episode of unprotected sex prior to the one that triggered her visit to the clinic.	Surgical termination
1/0302	17	Yes (two days after unprotected sex)	By 7-week ultrasound, conceived shortly after the index episode of unprotected sex.	Surgical termination
1/0362	16	Yes (two days after unprotected sex)	By 7-week ultrasound, conceived on or shortly after the index episode of unprotected sex.	Surgical termination
1/0384	16	Yes (one day after unprotected sex)	By 26-week ultrasound, conceived after the index episode of unprotected sex	Delivered healthy infant at 36.5 weeks gestation
1/0405	16	Yes (one day after unprotected sex)	By 7-week ultrasound, conceived on or shortly after the index episode of unprotected sex	Ongoing pregnancy
1/0502	16	Yes (one day after unprotected sex)	Negative pregnancy test two weeks after taking Plan B® One-Step; positive 3 weeks after taking Plan B® One-Step; therefore, likely conceived after the index episode of unprotected sex.	Miscarriage

Source: Dr. Furlong's review

[redacted] ll women who became pregnant used Plan B® One-Step as directed on the OTC labeling. It is important to remember that some pregnancies are expected to occur despite correct use: Plan B® One-Step reduces, but does not eliminate, the

chance of pregnancy after unprotected sex. In clinical trials, approximately 84% of expected pregnancies were prevented.

Assessment:

[redacted]

Postmarketing Spontaneous Reports

Refer to Dr. Christina Chang's review for a comprehensive look at the postmarketing safety databases. Of 69 countries in which levonorgestrel 1.5 mg is legally marketed, 32 market the product as a nonprescription drug. There have been no regulatory or marketing authorization actions taken for safety reasons, and the product has not been withdrawn from or restricted in any market for safety reasons. Between Jul-09 and Jan-11, approximately [redacted] ablets of Plan B® One-Step were distributed in the United States.

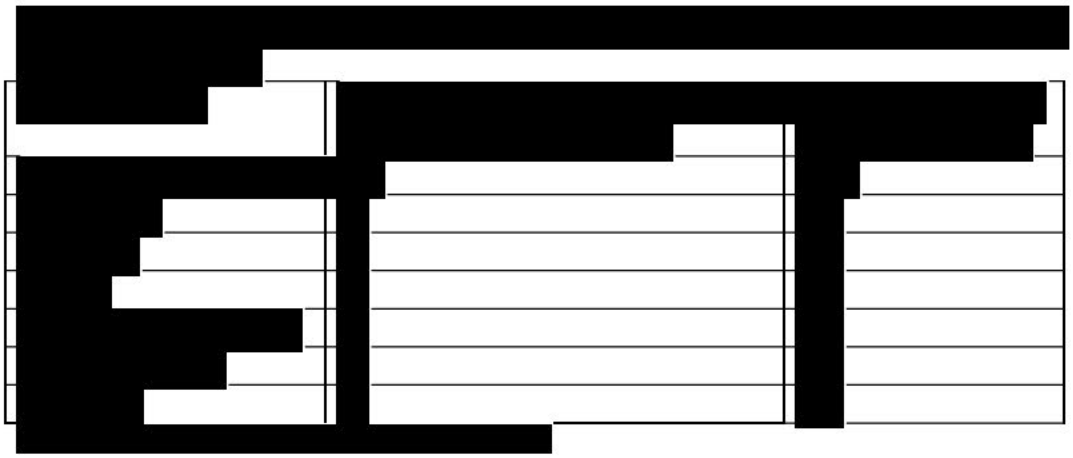
The applicant provided summaries of postmarketing reports from these databases:

- Teva's Internal Database (10-Jul-2009 through 30-Nov-2010)
- The World Health Organization (WHO) database (10-Jul-2009 through 15-Feb-2011)
- The FDA's AERS database (10-Jul-2009 through 30-Sep-2010)
- 120-day safety update
- DAWN
- AAPCC

[redacted] A brief summary of the postmarketing data by database follows.

Teva's Internal Database

[redacted]



WHO Database

The applicant requested a search of the WHO VigiBase for reports for levonorgestrel 1.5. mg from 10-Jul-2009 through 15-Feb-2011. A total of 369 cases reporting 969 events were obtained. Among these 369 cases, 5 were in adolescents aged 16 and under. No age specific adverse events were noted. Two of these cases overlapped with the AERS database. The remaining three reports were of breast disorder, ectopic pregnancy, and fetal abnormality (not otherwise specified).

AERS Database

The applicant conducted a search of the AERS database from July 10, 2009 to 30-Sep-2010 for Plan B®, Plan B® One-Step, and other levonorgestrel-containing emergency contraceptive products (ECs). For all women, there were 71 cases reporting 303 adverse events for Plan B® and Plan B® One-Step, and an additional 28 cases reporting 66 adverse events for other levonorgestrel ECs. A total of four cases were identified in young women aged 16 and under; all reporters were 15 or 16 years of age. The four cases reported hypersensitivity-type reaction, menstrual changes, emotional distress, lack of efficacy, nausea, vomiting, and hematemesis. There were no age specific adverse events.

120-Day Safety Update

DAWN and AAPCC

There is no historical evidence to suggest that levonorgestrel is a drug with abuse or even overuse potential. The DAWN database for 2004 – 2009 and the AAPCC database for 2008 and 2009 do not raise any new concerns.

Additional FDA Analyses of Postmarketing Data

During the Plan B® One-Step NDA supplement review, FDA performed a 915 review of Plan B® One-Step (Rubio). A 915 review occurs routinely 18 months after drug approval and exposure of at least 10,000 patients, whichever is later. This review for Plan B® One Step was a detailed look at postmarketing data by FDA's Office of Surveillance and Epidemiology and the Office of New Drugs, Division of Reproductive and Urologic Products (DRUP). The 915

review evaluated reports received for Plan B® One-Step from the time of approval in July, 2009 through January 2011. During the review it was found there were eighteen reports of hematemesis with both Plan B and Plan B One-Step and they were evaluated by Dr. Daniel Davis, a medical officer in the DRUP. Of these, five cases were in adolescents ages 15 – 17. These five cases are assessed in detail below. All of the eighteen cases were reported by consumers and none were confirmed by a healthcare professional. The 915 reviewers concluded [redacted]

Also, during the Plan B® One-Step NDA supplement review, the Office of Surveillance and Epidemiology (OSE) Division of Pharmacovigilance II was asked by Dr. M. Diane Murphy (Director, Office of Pediatric Therapeutics in the Office of the Commissioner) and Dr. Lisa Mathis to summarize postmarketing reports of adverse events associated with the use of Plan B® and Plan B® One-Step in patients ≤ 17 years of age. They requested this review in preparation for a routine, forthcoming meeting of the Pediatric Advisory Committee (PAC). The charge of the PAC (under the Food and Drug Administration Amendments Act) is to review safety data presented to them one year after a product is labeled under the Pediatric Research Equity Act and/or the Best Pharmaceuticals for Children Act, and to make recommendations on labeling based on those data. The FDA is charged with performing a review of all safety events since marketing, and providing that review to the PAC members so they can perform their function. This January 2012 meeting will address several approved products, among them Plan B® One-Step. The request for this OSE review was not triggered by any specific safety concern, but was simply triggered by the 2009 approval of Plan B® One-Step for pediatric use by prescription.

The OSE searched the AERS database for all reports of adverse events (serious and non-serious) from January 1, 2002 up to the "data lock" date of December 31, 2010. The AERS contained 252 reports for any Plan B® (levonorgestrel) formulation. Pediatric reports represented approximately 7.5% of the total (19/252). Eighteen of these were considered to be cases with a serious outcome. The November 10, 2011 OSE review (Miller, Rothstein, Scarazzini) described fatal outcomes or serious unlabeled adverse events with Plan B® (levonorgestrel, 0.75 mg) or Plan B® One-Step (levonorgestrel 1.5 mg). The OSE review was completed after Drs. Furlong and Chang completed their reviews and thus was not described by them, so I will describe it here and will shine a light on certain cases.

Premature Births and Spontaneous Abortions:
There were three reports of premature births. It is not clear that any of these women reported as having taken Plan B® were less than 18 years old. In these cases, the babies are reported as the pediatric patients, not the mothers. The long time between the taking of Plan B® by the mothers and the birth of the babies, makes it impossible to attribute causality to Plan B®. There is no other information about the mothers or maternal behavior provided in these case reports.

- One of the premature infants died when born at 5 months gestation. This was the only death reported among the 19 pediatric reports. The 31-year-old mother of this baby had taken Plan B on an unknown date in 12/2005 and the baby was born on [redacted] and died three days later.

- One mother (age unknown) took one dose of Plan B® on 1/7/09 and her baby, who was born on [redacted], did well.
- The third mother (age unknown) took only one dose of Plan B® on 03/08/09 (so she did not complete the dosing regimen) and she gave birth to her baby on [redacted]. This baby also did well.

Additionally, there were two cases of spontaneous abortion, one in a 16-year-old patient 6 weeks after taking Plan B® and the other in a 17-year-old patient less than 8 weeks after taking Plan B®. Levonorgestrel EC does not prevent all pregnancies, and the known rate of spontaneous abortions is high regardless of levonorgestrel EC use (up to 31% of pregnancies).[1] I think that Dr. Soule described this issue aptly in her 07/09/09 review of Plan B® One-Step when she stated that "given the known rate of spontaneous abortions (about 25% of all conceptions) the reports of spontaneous abortion *(with levonorgestrel EC)* are not unexpected and do not constitute a safety signal for this product." The rate of premature births is also high, approximately 11.5%[2] of all live births, and the same reasoning applies.

Hospitalizations:
The November 10, 2011 OSE review provided available details on three AE reports in adolescents that led to hospitalization and four cases of hematemesis, one of which resulted in a visit to the emergency room.

Here is my analysis regarding causality based upon the information received on three patients that were hospitalized:

- One 15-year-old patient took Plan B® on 09/11/07 and had a D & C-type procedure on 9/25/07 for cramping and vaginal bleeding that occurred on 09/24/07. It is not possible to attribute causality in this case.
- One 17-year-old patient, who had taken Plan B® on an unspecified date in October, 2008 was admitted to the hospital on [redacted] to treat an acetaminophen overdose. She was released the next day. It is not possible to say that this hospitalization is due to Plan B®.
- One 16-year-old experienced severe abdominal pain and vomiting in 2004 after taking her second dose of Plan B®. She was taken to the hospital where she was treated and released. This hospitalization may have been related to drug use, but the information in the report is too sparse to know for sure. Abdominal pain and vomiting are known, labeled, adverse effects of Plan B® in women of all ages.

Hematemesis Cases:
Next, I will highlight the five pediatric cases of hematemesis. (See Table 15.) (Four cases were reported in the November 10, 2011 OSE review and five were reported in the 915 review. This difference in the number of hematemesis cases derives from the fact that one case in the 915 review was reported in January 2011, after the data lock date for the OSE review.) These patients took Plan B® or Plan B® One-Step. One patient went to the emergency room (ER) but was not admitted. None of the others reported being seen at a hospital.

Table 15. Cases of Women Reporting Hematemesis

ISR Number	Age in Years	Medication Used	Other Details
6330193	16	Plan B® 08/19/09	Nausea and vomiting 08/19/10. Vomited blood on 08/21/09. Went to ER, not admitted. As of 08/24/09 vomiting continued but no more episodes of vomiting blood. There is insufficient information in the report to assess causality.
6408595	16	Plan B® One-Step 10/05/09	Vomited blood once on 10/19/09. Pregnancy test positive. Because of the timing of the vomiting and the positive pregnancy test, it is unlikely that the hematemesis was due to levonorgestrel.
5805767	15	Plan B® 06/22/08	One episode of hematemesis 06/26/08. Insufficient information in the report to assess causality.
6231375	17	Plan B® 06/06/09	One episode of vomiting which contained a small amount of blood 06/08/09. Insufficient information in the report to assess causality.
7210172 and 7231130	17	Plan B® One-Step 12/29/10	Vomited on 12/31/10, noticed a little tiny bit of blood and the event resolved the same day.

[redacted]

Syncope and Loss of Consciousness Cases:
As in other FDA safety reviews on levonorgestrel EC, in this OSE review there were rare reports (two) of syncope and (three) of loss of consciousness. [redacted]

[redacted]

Literature Review

9. Advisory Committee Meeting

On December 16, 2003, an Advisory Committee meeting was convened for NDA 21-045/S-011 to discuss the OTC switch of Plan B®. The committee voted overwhelmingly in favor of a complete OTC switch with no age restriction for Plan B®. The committee voted (27 to 1) that the Actual Use Study data could be generalized to the overall population of potential OTC users of Plan B®. They recommended that Plan B® be switched from prescription to OTC (23 to 4 with one member having left before voting) without age restriction. Since Plan B® and Plan B® One-Step are exceedingly similar drug products and no controversial data emerged from NDA 21-998 to generate the need for another advisory committee meeting, none was held. Likewise, no controversial data emerged from this efficacy supplement, so no Advisory Committee meeting was held.

10. Pediatrics

Dr. Lisa Mathis, Associate Director of the Pediatric and Maternal Health Staff in the Office of New Drugs, reviewed the data in this application at the consultative request of the Division of Nonprescription Clinical Evaluation. After completing her review, Dr. Mathis, a pediatrician, is recommending the approval of this application to expand OTC marketing to all females of child bearing potential. She comments that this product was previously determined to be safe and effective in the pediatric population as a prescription product. She comments that the new data submitted in the Label Comprehension and the Actual Use study provide the data to demonstrate that women of child bearing potential of all ages can appropriately self-diagnose and self-administer Plan B® One-Step in the OTC setting. She also states that no new safety concerns have been identified. Dr. Mathis states that the safety and efficacy of OTC Plan B® One-Step in the adolescent population is supported by the totality of data submitted to support the application.

Consistent with the Pediatric Review Committee recommendations from April 9, 2009, a partial waiver to study premenarcheal girls was previously granted to this sponsor because they are not at risk of becoming pregnant and the use of Plan B® One-Step would not be indicated.

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues.

[redacted]

12. Labeling

[redacted]

[redacted]

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

NDA 21-998/S002, Plan B® One-Step, should be approved OTC for women younger than 17 years of age with the agreed upon OTC Label and Consumer Information Leaflet as negotiated between DNCE and Duramed.

- Risk Benefit Assessment

Plan B® One-Step is to be taken as a single tablet as soon as possible within 72 hours of unprotected sexual intercourse to reduce the chance of pregnancy. It has been available OTC for women 17 years of age and older since 2009 and by prescription for those less than 17 years of age since 2009. With this efficacy supplement, Teva has sought to expand the OTC population for women less than 17 years of age. [redacted]

[redacted] The Code of Federal Regulations 21 CFR 310.200 states:

"Any drug limited to prescription use under section 503(b)(1)(B) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling."

Therefore, for a drug to be OTC, the labeling must convey the information needed to use the product safely and effectively in the absence of a healthcare practitioner. Reliance upon the product label to result in appropriate use is consistent with the tenet that the Agency has applied in the past and continues to apply when determining whether or not a product can be over-the-counter. It is an approach consistent with the regulations.

[redacted]

Division Director Review

[redacted]

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

[redacted]

- Recommendation for other Postmarketing Requirements and Commitments

[redacted]

References:

1. Wilcox AF, Weinberg CR, O'Connor JF, et al: Incidence of early loss of pregnancy. N Engl J Med 1988;319(4):189 - 94.

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3. Jueckstock JK, Kaestner R, Mylonas I: Managing hyperemesis gravidarum: a multimodal challenge. BMC Med 2010;8:46

4. Klebanoff, MA, Koslowe PA, Kaslow R, et.al: Epidemiology of Vomiting in Early Pregnancy. Obstet Gynecol 1985;66(5):612-616.

5. Monsour GM, Nashaat EH: Role of Helicobacter pylori in the pathogenesis of hyperemesis gravidarum. Arch Gynecol Obstet 2011;284(4):843-7.

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/s/

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11/30/2011